Volume 24 Supplement I May 1992

Journal of Molecular and Cellular Cardiology

Published for the International Society for

Heart Research

Program and Abstracts of the XIV World Congress of the International Society for Heart Research, Kobe, Japan, 10-14 May 1992

Academic Press
Harcourt Brace Jovanovich Publishers
London San Diego New York
Boston Sydney Tokyo Toronto
ISSN 0022-2828 JMCDAY 24(Suppl I) (1992)

O-18-2 INHIBITION OF NA^+/H^+ EXCHANGE PREVENTS VENTRICULAR FIBRILLATION AND PRESERVES FUNCTION IN PORCINE STUNNED MYOCARDIUM

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We investigated the effect of a new Na^+/H^+ inhibitor ((3-methylsulfonyl-4-piperidino-benzoyl)guanidine hydrochloride, HOE 694) on the incidence of ventricular fibrillation (VF), regional wall function (%SS) and ultrastructural changes (UC). Pigs were subjected to two 10' of left circumflex artery occlusion (CO) separated by 30' of reperfusion (REP) and followed by 4h of REP. The treated group (TRG) received the Na^+/H^+ inhibitor as a bolus (7mg/kg) 20' prior to CO and then by continuous infusion (0.07mg/kg). Control pigs (CON) received vehicle. During CO and REP, VF occurred in no pig out of 8 (0/8) in TRG, but in 9 of 11 (9/11) of CON ($p<0.001$). During REP, %SS of TRG was significantly less depressed than of CON:

%SS	REP 1h ($p<0.025$)	REP 2h ($p<0.05$)	REP 3h ($p<0.001$)	REP 4h ($p<0.005$)
CON %	49.0±4.4	51.5±5.2	49.5±4.6	50.9±5.4
TRG %	64.3±3.5	65.5±4.8	71.7±2.8	74.1±2.5

After CO and REP, UC were moderate and slightly abnormal in CON but much milder and completely recovered in TRG, respectively. We conclude that inhibition of sarcolemmal Na^+/H^+ exchanger is antiarrhythmogenic and diminishes myocardial ischemic cell injury.

O-18-3 ADULT AND IMMATURE RABBIT AND RAT HEARTS ARE TOLERANT TO REVERSIBLE MYOCARDIAL ISCHEMIC AND REPERFUSION INJURY "MYOCARDIAL STUNNING": ROLE OF 5'-NUCLEOTIDASE

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We determined if increased accumulation of AMP in rabbit and rat myocardium during ischemia (I) plays a role in myocardial tolerance to reversible I and reperfusion (R) injury. Isolated perfused adult rabbit (n=15) and rat (n=8) hearts were subjected to 15' of global ischemia (I) (37°C) and reperfused for 30'. Adenine nucleotides, nucleosides and purine bases were determined in myocardial biopsies using HPLC. Developed (DP) and end-diastolic pressure (EDP), coronary flow (CF) and ±dp/dt were monitored.

Rabbit Adenine Nucleotide Metabolites (nmol/mg Protein, *P<0.05 vs preischemia)

	Preischemia	Ischemia	Reperfusion
ATP	33.2±3	14.6±2*	23.3±1.0
AMP	1.3±0.4	12.3±2	0.8±0.2
Adenosine	0	*2.6+1	0

Recovery of hemodynamics were as follow:DP=120.4±3 vs 88.4±4; EDP= 3.8±0.3 vs 7.9±1; Coronary Flow = 36.3±1 vs 44.1±1; -dp/dt= -671±28 vs 481.0±14; and +dp/dt=1035±46 vs 702±26 (P=NS). Myocardial AMP in adult rat heart increased from 2.6±0.2 to 20.9±1.2 nmol/mg protein during 15' I. During R, ATP increased by 17 nmol/mg protein and ventricular function with concomitant reduction in AMP. Also, significant accumulation was noted during I in immature (1 day-old) rabbit (n=9) and rat (n=7) myocardium during global I in vitro. Recovery of myocardial ATP and increased tolerance of rabbit and rat myocardium to reversible I and R injury is related to species-, and age-related differences in entrapment of AMP during I which may be explained by either deficiency or inactivation of 5'-nucleotidase.

O-18-4 RAPID ATRIAL PACING FAILS TO PRECONDITION THE RABBIT HEART.

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Rapid Pacing has been shown to precondition the rabbit heart against ischaemic dysrrythmias (Sekeres et al .1991 JMCC: 23 ; S72). This study was designed to ascertain whether rapid pacing (RP) could also mimic ischaemic preconditioning (IP) when infarct size limitation was used as the endpoint.

NZW rabbits, 2.0-2.5kg, (n=5), were anaesthetised, ventilated and their hearts exposed via a left thoracotomy. The left atrium was paced at 420-480/min, whilst LV monophasic action potential (MAP), surface ECG and intra-arterial pressure (BP) were monitored. Faster RP invariably caused a precipitous drop in BP and VF. Five min of rapid pacing was followed by 10 min stabilization (to simulate an IP protocol), prior to coronary ligation for 45 min and reperfusion for 120 min. Infarct size was determined using tetrazolium and expressed as a percentage of the area at risk (I/R) demarcated by fluorescent microspheres.

RP caused an immediate drop in systolic BP from 91.4 ± 4.5 mmHg to 47.0 ± 5.9 mmHg ($p<0.0001$), diastolic BP from 67.2 ± 2.9mmHg to 23.6 ± 3.2mmHg ($p<0.0001$) which recovered within 30 secs of cessation of pacing. During RP the MAP duration shortened from 192 ± 13mS to 128 ± 5mS ($p=0.003$) and developed electrical alternans (n=4). Following RP the ECG showed either ST depression or T wave inversion (n=4). Despite these indirect indicators of myocardial ischaemia RP did not reduce infarct size v historical control (n=8), I/R 52.7 ± 4.6% v 58.2 ± 8.5% (p=NS) respectively.

Although RP produced evidence of ischaemia, no limitation of infarct size occurred. The failure of this technique to precondition the heart suggests that metabolite accumulation and/or washout, rather than an imbalance in myocardial metabolic supply and demand are necessary to cause ischaemic preconditioning.